

Rubella

THE NAME RUBELLA IS DERIVED FROM LATIN, MEANING “little red.” It was initially considered to be a variant of measles or scarlet fever and was called “third disease.” It was not until 1814 that it was first described as a separate disease in the German medical literature.

In 1914, Hess postulated a viral etiology based on his work with monkeys. Hiro and Tosaka in 1938 confirmed the viral etiology by passing the disease to children using filtered nasal washings from acute cases.

Following a widespread Australian epidemic of rubella infection in 1940, Gregg, an Australian ophthalmologist, reported in 1941 the occurrence of congenital cataracts among 78 infants born following maternal rubella infection in early pregnancy. This was the first reported recognition of congenital rubella syndrome (CRS).

Rubella Virus

Rubella virus was first isolated in 1962 by Parkman and Weller. Rubella virus is classified as a togavirus, genus *Rubivirus*. It is most closely related to group A arboviruses, such as Eastern and Western Equine Encephalitis viruses. It is an enveloped RNA virus, with a single antigenic type that does not cross-react with other members of the togavirus group.

Rubella virus is relatively unstable and is inactivated by lipid solvents, trypsin, formalin, ultraviolet light, extremes of pH and heat, and amantadine.

Rubella

- From Latin meaning "little red"
- Discovered in 18th century - thought to be variant of measles
- First described as distinct clinical entity in German literature
- Congenital rubella syndrome described by Gregg in 1941
- Pandemic in Europe and U.S. 1962-65

Rubella Virus

- Togavirus
- RNA virus
- One antigenic type
- Rapidly inactivated by chemical agents, low pH, heat and ultraviolet light

Rubella Pathogenesis

- Respiratory transmission of virus
- Replication in nasopharynx and regional lymph nodes
- Viremia 5-7 days after exposure with spread to tissues
- Placenta and fetus infected during viremia

Rubella Clinical Features

- Incubation period 12-23 days
- Lymphadenopathy in second week
- Maculopapular rash 14-17 days after exposure
- Rash on face and neck - may be more prominent after hot shower

Rubella Complications

Arthralgia or arthritis	
children	rare
adult female	up to 70%
Thrombocytopenic purpura	1/3000 cases
Encephalitis	rare
Neuritis	rare
Orchitis	rare

Pathogenesis

Following respiratory transmission of rubella virus, replication of the virus is thought to occur in the nasopharynx and regional lymph nodes. A viremia occurs 5-7 days after exposure with spread of the virus throughout the body. In CRS, transplacental infection of the fetus occurs during viremia. Fetal damage occurs through destruction of cells as well as mitotic arrest.

Clinical Features

Acquired rubella

The **incubation period** varies from 12 to 23 days.

Symptoms are often mild, and 30%-50% of cases may be subclinical or inapparent. In children, **rash** is usually the first manifestation and a prodrome is rare. In older children and adults, there is often a 1-5 day prodrome with low-grade fever, malaise, swollen glands, and upper respiratory infection (URI) preceding the rash. The rash of rubella usually occurs initially on the face and then progresses from head to foot. It lasts about 3 days and is occasionally pruritic. The rash is fainter than measles rash and does not coalesce.

Lymphadenopathy may begin 1 week before the rash and last several weeks. Postauricular, posterior cervical, and suboccipital nodes are commonly involved.

Arthralgia and arthritis occur so frequently in adults that they are considered by many to be an integral part of the illness as opposed to a complication. Other symptoms of rubella include conjunctivitis, testalgia, or orchitis. Forchheimer spots may be noted on the soft palate, but are not diagnostic for rubella.

Complications

Complications are uncommon, but tend to occur more often in adults than in children.

Arthritis or arthralgia may occur in up to 70% of adult women who contract rubella, but are rare in children or adult males. Fingers, wrists, and knees tend to be affected. Joint symptoms tend to occur about the same time or shortly after appearance of the rash and may last for up to 1 month; chronic arthritis is rare.

Encephalitis occurs in one in 5,000 cases, more frequently in adults (especially in females) than in children. Mortality estimates vary from 0 to 50%.

Hemorrhagic manifestations occur with an approximate incidence of 1 per 3,000 cases, occurring more often in children than in adults. These manifestations may be secondary to low platelets and vascular damage, with thrombocytopenic purpura being the most common manifestation. Gastrointestinal, cerebral, or intrarenal hemorrhage may occur. Effects may last from days to months, and most patients recover.

Additional complications include **orchitis**, **neuritis**, and a rare late syndrome of progressive **panencephalitis**.

Congenital Rubella Syndrome (CRS)

Prevention of CRS is the main objective of rubella vaccination programs in the United States.

The 1964 rubella epidemic resulted in 12.5 million cases of rubella infection and about 20,000 newborns with CRS. The estimated cost of the epidemic was \$840 million. This does not include the emotional toll on the families involved. The estimated lifetime cost of one case of CRS today is estimated to be in excess of \$200,000.

Rubella can be a disastrous disease in early gestation, leading to fetal death, premature delivery, and an array of congenital defects. Spontaneous abortion and stillbirths are common. The severity of the effects of rubella virus on the fetus depends largely on the time of gestation at which infection occurs. Up to 85% of infants infected in the first trimester of pregnancy will be found to be affected if followed after birth. While fetal infection may occur throughout pregnancy, defects are rare when infection occurs after the 20th week of gestation. The overall risk of defects during the third trimester is probably no greater than that associated with uncomplicated pregnancies.

Congenital infection with rubella virus can affect virtually all organ systems. **Deafness** is the most common and often the sole manifestation of congenital rubella infection, especially after the 4th month of gestation.

Eye defects, including cataracts, glaucoma, retinopathy, and microphthalmia may occur. **Cardiac defects** such as patent ductus arteriosus, ventricular septal defect, pulmonic stenosis, and coarctation of the aorta are possible. **Neurologic abnormalities**, including microcephaly and mental retardation, and other abnormalities, including bone lesions, splenomegaly, hepatitis, and thrombocytopenia with purpura may occur. Manifestations of CRS may be delayed from 2 to 4 years. Diabetes mellitus appearing in later childhood occurs frequently in children with CRS. In addition, progressive encephalopathy resembling subacute sclerosing panencephalitis (SSPE) has been observed in some older children with CRS.

Congenital Rubella Syndrome U.S. Epidemic 1964-1965

- 12.5 million rubella cases
- 2,000 encephalitis cases
- 11,250 abortions (surgical/spontaneous)
- 2,100 neonatal deaths
- 20,000 CRS cases
 - Deaf - 11,600
 - Blind - 3,580
 - Mentally retarded - 1,800

Congenital Rubella Syndrome

- Infection may affect all organs
- May lead to fetal death or premature delivery
- Infection early in pregnancy most dangerous (<12 weeks gestation)
- Organ specificity generally related to stage of gestational infection

Congenital Rubella Syndrome

- Deafness
- Cataracts
- Heart defects
- Microcephaly
- Mental retardation
- Bone alterations
- Liver and spleen damage

CRS infants may have low hemagglutination inhibition (HI) titers, but may have high titers of neutralizing antibody that may persist for years. Reinfection may occur. Impaired cell-mediated immunity has been demonstrated in some children with CRS.

Laboratory Diagnosis

Many rash illnesses may mimic rubella infection and up to 50% of rubella infections may be subclinical. The only reliable evidence of acute rubella infection is the presence of rubella-specific IgM antibody, demonstration of a significant rise in IgG antibody from paired acute and convalescent sera, or a positive viral culture for rubella.

Rubella Laboratory Diagnosis

- Isolation of rubella virus from clinical specimen (e.g., nasopharynx, urine)
- Significant rise in rubella IgG by any standard serologic assay (e.g., enzyme immunoassay)
- Positive serologic test for rubella IgM antibody

Rubella virus can be isolated from nasal, blood, throat, urine and cerebrospinal fluid specimens from rubella and CRS cases. Virus may be isolated from the pharynx 1 week before and until 2 weeks after rash onset. Although isolation of the virus is diagnostic of rubella infection, viral cultures are labor intensive and therefore, not done in many laboratories; they are generally not used for routine diagnosis of rubella. Viral isolation is an extremely valuable epidemiologic tool, and should be attempted for all suspected cases of rubella or CRS. A state laboratory or CDC should be consulted for details of viral isolation.

Serology is the most common method of confirming the diagnosis of rubella. Acute rubella infection can be serologically confirmed by a significant rise in rubella antibody titer in acute and convalescent serum specimens or by the presence of serum rubella IgM. Sera should be collected as early as possible (within 7–10 days) after onset of illness, and again 14–21 days (minimum of 7) days later.

False-positive serum rubella IgM tests have occurred in persons with parvovirus infections, with a positive heterophile test for infectious mononucleosis, or with a positive rheumatoid factor.

The serologic tests available for laboratory confirmation of rubella infections vary among laboratories. The state health department can provide guidance on available laboratory services and preferred tests.

Enzyme-linked immunosorbent assays (ELISA).

ELISA is sensitive, widely available, and relatively easy to perform. It can also be modified to measure IgM antibodies. Most of the diagnostic testing done for rubella antibodies uses some variation of ELISA.

Hemagglutination inhibition (HI) test was once the “standard” and most commonly used technique. It is sensitive and simple to perform and allows for either screening or diagnosis (if paired acute and convalescent sera are tested). A four-fold rise or greater in HI antibody titer in paired sera is diagnostic of recent infection. The test may be modified to detect rubella-specific IgM antibody indicative of primary infection.

Immunofluorescent antibody assay (IFA) is a rapid and sensitive assay. Commercial assays for both IgG and IgM are available in the United States. Care must be taken with the IgM assay to avoid false-positive results due to complexes with rheumatoid antibody.

Epidemiology

Occurrence

Rubella occurs worldwide.

Transmission

Rubella is spread from person-to-person via airborne transmission or droplets shed from the respiratory secretions of infected persons. There is no evidence of insect transmission.

Rubella may be transmitted by subclinical cases (approximately 30%-50% of all rubella infections).

Reservoir

Rubella is a human disease. There is no known animal reservoir. Although infants with CRS may shed rubella virus for an extended period, a true carrier state has not been described.

Temporal pattern

In temperate areas, incidence is usually highest in late winter and early spring.

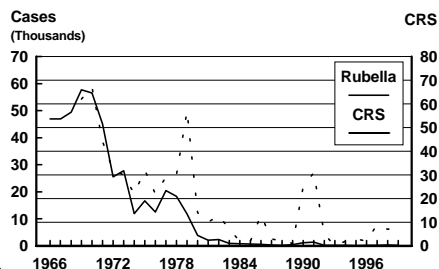
Communicability

Rubella is only moderately contagious. The disease is most contagious when the rash is erupting, but virus may be shed from 7 days before to 5-7 days or more after rash onset.

Infants with CRS shed large quantities of virus from body secretions for up to one year and can therefore transmit rubella to persons caring for them who are susceptible to the disease.

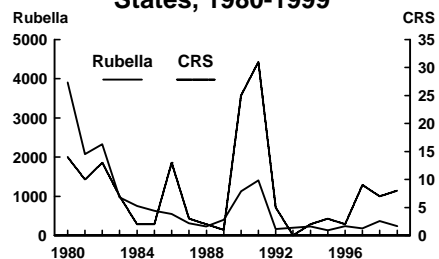
Rubella Epidemiology

• Reservoir	Human
• Transmission	Respiratory - person to person Subclinical cases may transmit
• Temporal pattern	Peak in late winter and spring
• Communicability	7 days before to 5-7 days after rash onset
	Infants with CRS may shed virus for a year or more

Rubella - United States, 1966-1999**Secular Trends in the United States**

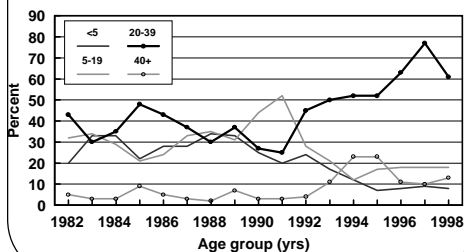
Rubella and congenital rubella syndrome became nationally notifiable diseases in 1966. The largest annual total of cases of rubella in the United States was in 1969, when 57,686 cases were reported (58 cases per 100,000 population).

Following vaccine licensure in 1969, rubella incidence fell rapidly. By 1983, fewer than 1,000 cases per year were reported (<0.5 cases per 100,000 population). A moderate resurgence of rubella occurred in 1990-1991, primarily due to outbreaks in California (1990) and among the Amish in Pennsylvania (1991).

Rubella and CRS - United States, 1980-1999

Until recently, there was no predominant age group for rubella cases. From 1982 through 1992, approximately 30% of cases occurred in each of three age groups: <5, 5-19, and 20-39 years. Adults >40 years of age typically accounted for <10% of cases. However, since 1994, persons 20-39 years of age have accounted for more than half of the cases. In 1997, this age group accounted for 77% of all reported cases.

Most reported rubella in the U.S. since the mid-1990s has occurred among Hispanic young adults who were born in areas where rubella vaccine is not routinely given.

Rubella - United States, 1982-1998 Age Distribution of Reported Cases

In the prevaccine era, epidemics of rubella occurred every 6-9 years, with the last major U.S. epidemic occurring in 1964-1965. No large epidemics have occurred since the vaccine was licensed for use in 1969. However, outbreaks continue to occur among groups of susceptible persons who congregate in locations that increase their exposure and among persons with religious and philosophic exemption to vaccination. Several recent outbreaks have occurred in workplaces where most employees are foreign-born, particularly from Latin America.

Rubella and CRS in the United States, 1990s

- Most reported rubella in the U.S. since the mid-1990s has occurred among Hispanic young adults
- Rubella outbreaks have occurred in workplaces where most employees are foreign-born
- All CRS since 1996 has occurred in children of unvaccinated women born Latin America

CRS surveillance is maintained through the National Congenital Rubella Registry, which is managed by the National Immunization Program. The largest annual total of reported CRS cases to the registry was in 1970 (67 cases). An average of 5-6 CRS cases have been reported annually since 1980. Although reported rubella activity has consistently and significantly decreased since vaccine has been used in the U.S., the incidence of CRS has only paralleled the decrease in rubella cases since the mid-1970s. The fall in CRS since the mid-1970's was due to an increased effort to vaccinate susceptible adolescents and young adults, especially women.

Rubella outbreaks are almost always followed by an increase in CRS. Rubella outbreaks in California and Pennsylvania in 1990-1991 resulted in 25 cases of CRS in 1990 and 33 cases in 1991. A provisional total of 8 CRS cases were reported in 1999. The mothers of these infants were born outside the United States, primarily in Latin America and the Caribbean where rubella vaccine is not routinely used.

Classification of Rubella Cases

Clinical case definition of acquired rubella

A clinical case of rubella is defined as an illness with all of the following characteristics: (1) acute onset of generalized maculopapular rash; (2) a temperature $>37.2^{\circ}\text{C}$ ($>99^{\circ}\text{F}$), if measured; and (3) arthralgia, arthritis, lymphadenopathy, or conjunctivitis. Cases meeting the measles case definition are excluded. Also excluded are cases with serology compatible with recent measles virus infection.

Case classification of acquired rubella

A **suspected case** is any generalized rash illness of acute onset. A **probable case** meets the clinical case definition, has noncontributory or no serologic or virologic testing, and is not epidemiologically linked to a laboratory confirmed case. A **confirmed case** is laboratory confirmed or meets the clinical case definition and is epidemiologically linked to a laboratory confirmed case.

Clinical case definition of congenital rubella syndrome (CRS)

The clinical case definition of CRS is an illness, usually diagnosed in infancy, resulting from rubella infection *in utero* and characterized by symptoms from the following categories:

(A) Cataracts, congenital glaucoma, congenital heart disease (most commonly patent ductus arteriosus or peripheral pulmonary artery stenosis), loss of hearing, pigmentary retinopathy

Associated symptoms may be:

(B) Purpura, splenomegaly, jaundice, microcephaly, mental retardation, meningoencephalitis, radiolucent bone disease.

Rubella Case Definition

Clinical case definition

Acute onset of generalized maculopapular rash
Temperature $>37.2^{\circ}\text{C}$ ($>99^{\circ}\text{F}$), if measured
Arthralgia/arthritis, or lymphadenopathy, or conjunctivitis

Laboratory criteria for diagnosis

- Isolation of rubella virus, or
- Significant increase in rubella IgG antibody level between acute and convalescent samples, or
- Positive serologic test for rubella IgM antibody

Case classification of congenital rubella syndrome

An infection-only case is one with laboratory evidence of infection, but without any clinical symptoms or signs. A **suspected case** has some compatible clinical findings, but does not meeting the criteria for a probable case. A **probable case** is one that is not laboratory confirmed, has any two complications listed in (A) above or one complication from (A) and one from (B), and lacks evidence of any other etiology. A **confirmed case** is a clinically compatible case and is laboratory confirmed. In probable cases, either or both of the eye-related findings (cataracts and congenital glaucoma) count as a single complication. In cases classified as infection-only, if any compatible signs or symptoms (*e.g.*, hearing loss) are identified later, the case is reclassified as confirmed.

Rubella Vaccine

Three rubella vaccines were licensed in the U.S. in 1969: HPV-77:DE-5 (duck embryo), HPV-77:DK-12 (dog kidney), and Cendehill (rabbit kidney) strains. The HPV-77:DK-12 was later removed from the market because there was a higher rate of joint complaints following vaccination with this strain. In January 1979, the RA 27/3 (human diploid fibroblast) strain (Meruvax-II) was licensed and all other strains were discontinued.

Rubella Vaccine

Vaccine	Trade Name	Licensure
GMK-3:RK53	Cendevax	1969
HPV-77:DK12	Rubelogen	1969
HPV-77:DE5	Meruvax	1969
RA 27/3*	Meruvax II	1979

*Only currently licensed vaccine in U.S.

Characteristics

The RA 27/3 rubella vaccine is a live attenuated virus. It was first isolated in 1965 at the Wistar Institute from a rubella-infected aborted fetus. The virus was attenuated by 25-30 passages in tissue culture, using human diploid fibroblasts. It does not contain duck, chicken or egg protein.

Vaccine virus is not communicable, except in the setting of breast-feeding (see below), even though virus may be cultured from the nasopharynx of vaccinees.

Immunogenicity and vaccine efficacy

Rubella vaccine is available as a single antigen preparation, combined with mumps vaccine, or combined with measles and rubella vaccines. The ACIP recommends that combined measles-mumps-rubella vaccine (MMR) be used when any of the individual components is indicated.

RA 27/3 rubella vaccine is safe and more immunogenic than previously used rubella vaccines. In clinical trials, 95% or more of vaccinees aged 12 months and older developed serologic evidence of rubella immunity after a

Rubella Vaccine

- **Composition** Live virus (RA 27/3 strain)
 - **Efficacy** 95% (Range, 90%-97%)
 - **Duration of Immunity** Lifelong
 - **Schedule** 1 Dose \geq 12 months of age
- Should be administered with measles and mumps as MMR

single dose. More than 90% of vaccinated persons have protection against both clinical rubella and viremia for at least 15 years. Follow-up studies indicate that one dose of vaccine confers long-term, probably lifelong, protection.

Several reports indicate that viremic reinfection following exposure may occur among vaccinated persons who have low levels of detectable antibody. The frequency and consequences of this phenomenon are unknown, but it is believed to be uncommon. Rarely, clinical reinfection and fetal infection have been reported among women with vaccine-induced immunity. Rare cases of CRS have occurred among infants born to women who had documented serologic evidence of rubella immunity before they became pregnant.

Vaccination Schedule and Use

Two doses of rubella vaccine, as combination MMR vaccine, separated by at least 4 weeks, are routinely recommended for all children. All persons born in or after 1957 should have documentation of at least one dose of MMR. The **first dose of MMR** should be given on or after the first birthday. Any dose of rubella-containing vaccine given before 12 months of age should not be counted as part of the series. Children vaccinated with rubella-containing vaccine before 12 months of age - even one day early - should be revaccinated with two doses of MMR vaccine, the first of which should be administered when the child is at least 12 months of age.

A **second dose of MMR** is recommended to produce immunity in those who failed to respond to the first dose. Data indicate that almost all of the persons who do not respond to the measles component of the first dose will respond to a second dose of MMR. Few data on the immune response to the rubella and mumps components of a second dose of MMR are available. However, most persons who do not respond to the rubella or mumps component of the first MMR dose would be expected to respond to the second dose of MMR. The second dose is not generally considered a booster dose because a primary immune response to the first dose provides long-term protection. Although a second dose of vaccine may increase antibody titers in some persons who responded to the first dose, available data indicate that these increased antibody titers were not sustained. The combined MMR vaccine is recommended for both doses to assure immunity to all three viruses.

The second dose of MMR vaccine should routinely be given at age 4-6 years, before a child enters kindergarten or first grade. The adolescent health visit at age 11-12 years can serve as a catch-up opportunity to verify vaccination

Indications for Rubella (MMR) Vaccine

- All infants >12 months of age
- Susceptible adolescents and adults without documented evidence of rubella immunity
- Emphasis on non-pregnant women of childbearing age

status and administer MMR vaccine to those children who have not yet received two doses of MMR (with the first dose administered no earlier than the first birthday). The second dose of MMR may be administered as soon as one month (*i.e.*, minimum of 28 days) after the first dose.

All older children not previously immunized should receive one dose of rubella vaccine as MMR.

Adults born in 1957 or later who do not have a medical contraindication should receive at least one dose of MMR vaccine unless they have documentation of vaccination with at least one dose of measles-, rubella-, and mumps-containing vaccine or other acceptable evidence of immunity to these three diseases. Some adults at high risk of measles exposure may require a second dose of measles vaccine. This second dose should be administered as combined MMR vaccine (see Measles chapter for details).

Efforts should be made to identify and vaccinate susceptible adolescents and adults, particularly women of childbearing age who are not pregnant. Particular emphasis should be placed on vaccinating both males and females in colleges, places of employment, and health care settings.

Rubella immunity

Rubella Immunity

- Documentation of at least one dose of rubella-containing vaccine
- Serologic evidence of immunity
- Born before 1957 (except women of childbearing age)

Persons generally can be considered immune to rubella if they have documentation of vaccination with at least one dose of MMR or other live rubella-containing vaccine administered on or after their first birthday, have laboratory evidence of rubella immunity, or were born before 1957. Persons who have an “equivocal” serologic test result should be considered rubella-susceptible unless they have evidence of adequate vaccination or subsequent serologic testing indicates rubella immunity. Although only one dose of rubella-containing vaccine is required as acceptable evidence of immunity to rubella, children should receive two doses of MMR vaccine according to the routine childhood vaccination schedule.

Birth before 1957 provides only presumptive evidence of rubella immunity; it does not guarantee that a person is immune to rubella. Because rubella can occur in some unvaccinated persons born before 1957 and because congenital rubella and congenital rubella syndrome can occur in the offspring of women infected with rubella during pregnancy, **birth before 1957 is not acceptable evidence of rubella immunity for women who might become pregnant.**

Clinical diagnosis of rubella is unreliable and should not be considered in assessing immune status. Because many rash illnesses may mimic rubella infection and many rubella infections are unrecognized, the only reliable evidence of previous rubella infection is the presence of serum rubella IgG. Laboratories that regularly perform antibody testing are generally the most reliable because their reagents and procedures are strictly standardized.

Occasionally, an individual with a history of documented rubella vaccination is found to have a negative serum IgG by ELISA. Such persons may be given a dose of MMR vaccine and do not need to be retested for serologic evidence of rubella immunity.

Although birth before 1957 is generally considered acceptable evidence of measles and rubella immunity, medical facilities should consider recommending a dose of MMR vaccine to unvaccinated workers born before 1957 who do not have laboratory evidence of rubella immunity. Rubella vaccination or laboratory evidence of rubella immunity is particularly important for health-care workers who could become pregnant, including those born before 1957. This recommendation is based on serologic studies which indicate that among hospital workers born before 1957, 5-9% had no detectable measles antibody.

Serologic screening need not be done before vaccinating for measles and rubella unless the medical facility considers it cost-effective. Serologic testing is appropriate only if tracking systems are used to ensure that tested persons who are identified as susceptible are subsequently vaccinated in a timely manner. If the return and timely vaccination of those screened cannot be assured, vaccination should be performed without prior testing. Serologic testing for immunity to measles and rubella is not necessary for persons documented to be appropriately vaccinated or who have other acceptable evidence of immunity.

Neither rubella vaccine nor immune globulin is effective for **post-exposure prophylaxis of rubella**. Vaccination after exposure is not harmful and may possibly avert later disease.

Adverse Reactions Following Vaccination

Rubella is a very safe vaccine. Most adverse events reported following MMR vaccination are attributable to the measles component (such as fever and rash). The most common complaints following rubella vaccination are fever, lymphadenopathy, and arthralgia. These adverse events only occur in susceptible persons and are more common in adults, especially in women.

MMR Adverse Reactions

• Fever	5%-15%
• Rash	5%
• Joint symptoms	25%
• Thrombocytopenia	<1/30,000 doses
• Parotitis	rare
• Deafness	rare
• Encephalopathy	<1/1,000,000 doses

Rubella Vaccine Arthropathy

- Acute joint symptoms in about 25% of susceptible adult women
- Frank arthritis occurs in about 10%
- Rare reports of chronic or persistent symptoms

Joint symptoms, such as arthralgia (joint pain) and arthritis (joint redness and/or swelling), are associated with the rubella component of MMR. Arthralgia and transient arthritis occur more frequently in susceptible adults than in children and more frequently in susceptible women than in men. Acute arthralgia or arthritis are rare following vaccination of children with RA 27/3 vaccine. By contrast, approximately 25% of susceptible postpubertal females develop acute arthralgia following RA 27/3 vaccination, and approximately 10% have been reported to have acute arthritis-like signs and symptoms. Rarely, transient peripheral neuritic complaints, such as paresthesias and pain in the arms and legs, have been reported.

When acute joint symptoms occur, or when pain and/or paresthesias not associated with joints occur, the symptoms generally begin 1-3 weeks after vaccination, persist for 1 day to 3 weeks, and rarely recur. Adults with acute joint symptoms following rubella vaccination rarely have had to disrupt work activities.

Data from studies in the United States and experience from other countries using the RA 27/3 strain rubella vaccine have not supported an association between the vaccine and chronic arthritis. One study among 958 seronegative immunized and 932 seronegative unimmunized women aged 15-39 years found no association between rubella vaccination and development of recurrent joint symptoms, neuropathy, or collagen disease.

The ACIP continues to recommend the vaccination of all adult women who do not have evidence of rubella immunity.

Contraindications and Precautions to Vaccination

MMR Vaccine Contraindications and Precautions

- Severe allergic reaction to prior dose or vaccine component
- Pregnancy
- Immunosuppression
- Moderate or severe acute illness
- Recent blood product

Persons who have experienced a **severe allergic reaction** (i.e., hives, swelling of the mouth or throat, difficulty breathing, hypotension, shock) following a prior dose of rubella vaccine or to a vaccine component (e.g., gelatin, neomycin), should generally not be vaccinated with MMR.

Women known to be pregnant or attempting to become pregnant should not receive rubella vaccine. Although there is no evidence that rubella vaccine virus causes fetal damage (see below), pregnancy should be avoided for 3 months after rubella or MMR vaccination.

Persons with **immunodeficiency or immunosuppression**, resulting from leukemia, lymphoma, generalized malignancy, immune deficiency disease, or immunosuppressive therapy should not be vaccinated. However, treatment with low dose (<2 mg/kg/day), alternate day, topical, or aerosolized steroid preparations is not a contraindication to rubella vaccination. Persons whose immunosuppressive therapy with steroids has been stopped for 1 month (3 months for chemotherapy) may be vaccinated. Rubella vaccine should be considered for persons with HIV infection.

Persons with **moderate to severe acute illness** should not be vaccinated until the illness has resolved. Minor illness (*e.g.*, otitis media, mild upper respiratory infections), concurrent antibiotic therapy, and exposure or recovery from other illness are not contraindications to rubella vaccination.

Receipt of antibody-containing blood products (*e.g.*, immune globulin, whole blood or packed red blood cells, intravenous immune globulin) may interfere with seroconversion to rubella vaccine. Vaccine should be given 2 weeks before, or deferred for at least 3 months following administration of an antibody-containing blood product. If rubella vaccine is given as combined MMR, a longer delay may be necessary before vaccination. For more information, see the chapter on General Recommendations on Immunization.

Previous administration of human anti-Rho(D) immune globulin (RhoGam) does not generally interfere with an immune response to rubella vaccine and is not a contraindication to postpartum vaccination. However, women who have received anti-Rho immune globulin should be serologically tested 6-8 weeks after vaccination to assure that seroconversion has occurred.

Although vaccine virus may be isolated from the pharynx, vaccinees do not transmit rubella to others, except occasionally in the case of the vaccinated breast-feeding woman. In this situation, the infant may be infected, presumably through breast milk, and may develop a mild rash illness, but serious effects have not been reported. Infants infected through breast-feeding have been shown to respond normally to rubella vaccination at 12-15 months of age. Breast-feeding is not a contraindication to rubella vaccination and does not alter rubella vaccination recommendations.

Rubella Vaccination of Women of Childbearing Age

Rubella Vaccination of Childbearing-Age Women

- Ask if pregnant or likely to become so in next 3 months
- Exclude those who say "yes"
- For others
 - Explain theoretical risks
 - Vaccinate

Women who are pregnant or intend to become pregnant within 3 months, should not receive rubella vaccine. The Advisory Committee on Immunization Practices (ACIP) recommends that vaccine providers ask a woman if she is pregnant or likely to become pregnant in the next 3 months. Those who are pregnant or intend to become pregnant should not be vaccinated. All other women should be vaccinated after being advised of the theoretical risks of vaccination during pregnancy and the importance of not becoming pregnant during the 3 months following vaccination. ACIP does not recommend routine pregnancy screening of women before rubella vaccination.

If a pregnant woman is inadvertently vaccinated or if she becomes pregnant within 3 months after vaccination, she should be counseled about the concern for the fetus (see below), but MMR vaccination during pregnancy should not ordinarily be a reason to consider termination of the pregnancy.

While pregnancy is a contraindication to rubella vaccination, some women have been inadvertently vaccinated while pregnant or soon before conception. When rubella vaccine was licensed, this situation was of concern because of the known teratogenicity of the wild virus strain. To define the risk, if any, the Centers for Disease Control and Prevention (CDC) maintained a registry of women vaccinated during pregnancy to determine whether CRS would occur in infants of such mothers from 1971-1989.

Rubella Vaccination in Pregnancy Study 1971-1989

- 321 women enrolled
- 324 live births
- No observed CRS
- 95% confidence limits 0%-1.2%

Subclinical fetal infection has been detected serologically in approximately 1%-2% of infants born to susceptible vaccinees, regardless of the vaccine strain. However, based on data collected by the CDC in the **Vaccine in Pregnancy (VIP) Registry (1971-1989)**, no evidence of CRS has occurred in offspring of the 321 susceptible women who received rubella vaccine and who continued pregnancy to term. The observed risk of vaccine-induced malformation is now 0%, with a maximum theoretical risk of 1.6%, based on 95% confidence limits (1.2% for all types of rubella vaccine). Since the risk of the vaccine to the fetus appears to be extremely low, if it exists at all, routine termination of pregnancy is not recommended. Individual counseling for these women is recommended. As of April 30, 1989, CDC discontinued the VIP registry.

Evaluation of the effectiveness of prevaccine pregnancy prevention counseling in women of childbearing age in Hawaii revealed that the pregnancy rate for all women 15-44 years old in Hawaii was 122.8/1,000/year and the pregnancy rate among vaccinees 15-44 years of age who were counseled was 14.0/1,000/year. The efficacy of counseling is 88.6% ($(122.8-14.0)/(122.8 \times 100)$).

The ACIP continues to state that pregnant women should **not** be vaccinated, because of the small theoretical risk to the fetus of a vaccinated woman.

Vaccine Storage and Handling

Measles-mumps-rubella (MMR) vaccine must be shipped with refrigerant to maintain 10°C (50°F) or less at all times. Vaccine must be refrigerated immediately on arrival and protected from light at all times. The vaccine must be stored at refrigerator temperature (2°-8°C [35°-46°F]), but may be frozen. Diluent may be stored at refrigerator temperature or at room temperature.

After reconstitution, MMR vaccines must be stored at refrigerator temperature and protected from light. Reconstituted vaccine should be used immediately. If reconstituted vaccine is not used within 8 hours it must be discarded.

Strategies to Decrease Rubella and CRS

CRS elimination

Although the CRS case count is low, rubella transmission continues to occur, and increased in 1989 and 1990. The elimination of CRS will require several interventions:

- Achievement and maintenance of high immunization levels.
- Intensive surveillance of rubella and CRS.
- Prompt outbreak control when rubella occurs.

Vaccination of susceptible postpubertal females

Perhaps the final frontier in conquering rubella and CRS can be reached by expanding and intensifying efforts to vaccinate susceptible adolescents and young adults of childbearing age, particularly those born outside the United States.

Rubella Vaccine Recommendations for Increasing Coverage

- Continued routine vaccination of children at >12 months with vaccination required for school entry
- Screen and vaccinate susceptibles
 - Health care workers
 - College entry
 - Premarital
 - Prenatal with postpartum vaccination
 - Other health care visits

These efforts should include vaccinating in family planning clinics, sexually transmitted disease (STD) clinics, and as part of routine gynecologic care; maximizing use of premarital serology results; emphasizing immunization for college students; vaccinating women postpartum and postabortion; and immunizing prison staff, and when possible, prison inmates, especially women inmates.

Hospital rubella programs

Emphasis should be placed on vaccinating susceptible hospital personnel, both male and female (volunteers, trainees, nurses, physicians, etc.) Ideally, all hospital employees should be immune. It is important to note that screening programs alone are not adequate. Vaccination of susceptible staff must follow.

Use of combination vaccines

The hope is that use of combination vaccines such as MR and MMR vaccines and the two-dose schedule of MMR vaccine for measles control will increase the level of rubella seropositivity in children and adults. Persons already immune to rubella should not have adverse events attributable to rubella vaccine; those not already immune are in need of vaccination against rubella.

Summary - Rubella

- Congenital rubella syndrome
- Increase efforts to vaccinate childbearing-age women
- Included in 2 dose recommendation for measles
- Arthropathy

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